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An international survey of management of pain and sedation after paediatric cardiac surgery

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ABSTRACT

Objective The mainstay of pain treatment after paediatric cardiac surgery is the use of opioids. Current guidelines for its optimal use are based on small, non-randomised clinical trials, and data on the pharmacokinetics (PK) and pharmacodynamics (PD) of opioids are lacking. This study aims at providing an overview of international hospital practices on the treatment of pain and sedation after paediatric cardiac surgery.

Design A multicentre survey study assessed the management of pain and sedation in children aged 0–18 years after cardiac surgery.

Setting Pediatric intensive care units (PICU)of 19 tertiary children's hospitals worldwide were invited to participate. The focus of the survey was on type and dose of analgesic and sedative drugs and the tools used for their pharmacodynamic assessment.

Results Fifteen hospitals (response rate 79%) filled out the survey. Morphine was the primary analgesic in most hospitals, and its doses for continuous infusion ranged from 10 to 60 mcg kg^{-1} h^{-1} in children aged 0–36 months. Benzodiazepines were the first choice for sedation, with midazolam used in all study hospitals. Eight hospitals (53%) reported routine use of sedatives with pain treatment. Overall, type and dosing of analgesic and sedative drugs differed substantially between hospitals. All participating hospitals used validated pain and sedation assessment tools.

Conclusion There was a large variation in the type and dosing of drugs employed in the treatment of pain and sedation after paediatric cardiac surgery. As a consequence, there is a need to rationalise pain and sedation management for this vulnerable patient group.

What is already known on this topic?

- There is large variability in choice and dosing of analgesics and sedatives after cardiac surgery in children worldwide.
- Validated pain and sedation tools were used extensively.

What this study hopes to add?

- Insight into clinical protocols on use of analgesics and sedatives in children after cardiac surgery, showing large variability in choice and dosing of analgesics and sedatives.
- Morphine is the first choice analgesic, while midazolam is the first choice sedative. Dosing of both drugs differ considerably between hospitals.
- Use of validated pharmacodynamics (PD) assessment tools is not standard in clinical practise. Lack of a validated PD assessment tool could result in oversedation.

INTRODUCTION

Congenital heart disease accounts for almost one-third of all congenital defects.[1] Adequate postoperative sedation and pain management is important in these patients because untreated pain can lead to a delayed recovery, prolonged adverse behavioural consequences and negative physiological responses.[2–4]

Morphine is widely used for analgesia after major surgery in neonates and children. Several studies on morphine pharmacokinetics (PK)/pharmacodynamics (PD) have resulted in age-specific dosing algorithms in children after non-cardiac surgery. Ceelie *et al* showed equipotency of paracetamol as primary analgesic as compared with morphine in neonates and children <1 year of age after major non-cardiac surgery. It is currently unclear if these data can be extrapolated to children after cardiac surgery.[5 6]

Postoperative analgosedation in children after cardiac surgery is mainly achieved with opioids combined with sedatives. The most common opioid used is morphine, with doses ranging from 5 to 80 mcg/kg/h.[7] Morphine is recommended as drug of first choice by the Association of Paediatric Anaesthetists of Great Britain and Ireland.[8] However, this guideline is based on small, non-randomised clinical trials. PK data are available

for the routinely prescribed analgesics and sedatives, but combined PK/PD data are scarce.

Lynn *et al* described adequate pain relief after cardiac surgery with continuous morphine infusions of 10–38.5 mcg/kg/h. [9 10] Even though adequate analgesia can be achieved, plasma morphine concentrations above 20 ng/mL have been associated with adverse effects, such as hypotension and respiratory depression.[9 11] Patients with cyanotic heart defects showed lower morphine requirements and higher plasma concentrations compared with patients with non-cyanotic heart defects, indicating that type of defect or type of surgery may be associated with altered PK/PD necessitating different dosing regimens.[12]

A recent review by Lucas *et al*[13] on pharmacotherapies in paediatric cardiac critical care provides an extensive overview of PK of analgesic and sedative drugs used in children after cardiac surgery but focused less on their use in protocols for clinical practice. Changes in clearance and volume of distribution (PK) and/or PD due to the use of cardiopulmonary bypass (CPB), disease processes, low cardiac output syndrome, surgical procedure and age may alter optimal way of dosing analgesics and sedatives in children after cardiac surgery.[14] These expected PK/PD differences are not incorporated in existing guidelines, and it is unclear if they are introduced into local protocols.

While current dosing is commonly titrated to effect (sedation or pain score), quantification of that effect can be difficult as pain, and sedation scores are not always validated for different patient groups. A one-size-fits-all dosing regimen may lead to oversedation or undersedation resulting in less efficacy or increased toxicity. As clear individualised evidence-based dosing guidelines are lacking, a wide variety can be expected in clinical practice.

Our primary objective was to ascertain international analgosedation practices after paediatric cardiac surgery with a self-reported survey. Our main focus was the use of local protocols, choice and dosing range of analgesics and sedatives, use of pain and sedation scores and the use of treatment algorithms.

METHODS

Design

A self-designed web-based survey (Monkey Survey, https://nl.surveymonkey.com/) was circulated to medical specialists in tertiary cardiac care hospitals who are responsible for the treatment of children after cardiac surgery. Hospitals were selected based on expertise and yearly conduct of more than 150 paediatric on-pump cardiac surgical procedures. The survey was designed by a small focus group consisting of a congenital cardiothoracic surgeon, three paediatric intensivists and a paediatric cardiac anaesthesiologist because of the absence of validated questionnaires. The potential respondents were instructed that this survey aimed at collecting data on the current treatment strategies concerning the use of analgesics and sedatives, as well as the tools used for the measurement of pain and sedation, according to their local protocols and not their personal preference. The survey has been provided in the appendix.

The survey focused primarily on the choice and dosing regimens of analgesic and sedative drugs prescribed in the surveyed institutions as well as the PD assessment tools that were used in these circumstances. Additional questions related to the characteristics of the unit.

Potential participants initially received a letter asking for their involvement in the survey. If they agreed, details of the survey as well as the link to enter their answers were provided by email. If necessary, an additional email to remind the participants about the survey was sent 2 and 4 weeks after the initial letter. Data were collected between June and August 2014.

Ethical approval was not needed for this study, since no patients are involved neither person-related questions are raised to the individual hospitals.

RESULTS

Hospital characteristics

A total of 19 hospitals on three different continents were willing to participate; 15 (response rate 79%) hospitals completed the survey in full. Twelve respondents (80%) were from European hospitals. Three respondents were from non-European hospitals based in New Zealand, Australia and Canada. Non-respondents were based in the USA (n=1), UK (n=2) and China (n=1). Respondents were physicians, mainly paediatric intensivists or paediatric cardio-anaesthesiologists who work in paediatric cardiac critical care units. Two paediatric intensivists reported that they had consulted a paediatric cardio-anaesthesiologist on questions relating to the perioperative management.

The participating hospitals perform a total of over 3000 on-pump paediatric cardiosurgical procedures annually with a postoperative ICU stay ranging between 2 and 7 days.

The number of procedures per age category varied between hospitals; however, about two-third of the procedures were performed in children under the age of 1 year.

Medication

Table 1 shows the type and dosing of reported analgesics. Table 2 shows the type and dosing of reported sedatives. Both tables show the results for treatment protocol in neonates and children until the age of 2 years. There was a wide range of choices and dosing regimens of drugs reported for both analgesics and sedatives. Moreover, polypharmacy is often used to accomplish the desired effects for both analgesia and sedation. Eleven different analgesics and eight different sedatives were reported.

None of the hospitals based analgosedation according to protocol on cardiac diagnosis, severity scores or type of surgery. One hospital added fentanyl for analgesic

Table 1 Results of the international survey for type and dose of analgesics in children after cardiac surgery

	Neonates 0–28 days		Infants 29 days–2 years	
Medication	**Use in hospitals (n)**	**doses**	**Use in hospitals (n)**	**doses**
Morphine IV bolus mcg/kg	9	50–200	9	50–500
Morphine IV mcg/kg/h	12	5–40	12	10–60
Piritramide IV bolus mg/kg	1	0.2–1.2	2	0.05–0.4
Piritramide IV mg/kg/day	n.a.	n.a.	1	1.2
Fentanyl IV bolus mcg/kg	1	1–2	1	1–2
Fentanyl IV mcg/kg/h	3	1–6	3	1–6
Remifentanil IV bolus mcg/kg	1	1	1	1
Remifentanil IV mcg/kg/min	1	0.1–0.2	1	0.1–0.2
Sufentanil IV mcg/kg/h	1	1–2	1	1–2
Dexmedotomidine IV bolus mcg/kg	n.a.	n.a.	1	50
Dexmedetomidine IV mcg/kg/h	n.a.	n.a.	2	0.5–1.5
Paracetamol IV mg/kg	5	7.5	7	7.5–15
Paracetamol PO/PR mg/kg/day	5	45–90	7	45–90
Metamizol IV mg/kg	1	40	1	40
Diclofenac IV/PR mg/kg/day	n.a.	n.a.	3	1–3
Ibuprofen PO bolus mg/kg	n.a.	n.a.	2	5–10
Dexketoprofen IV mg/kg	1	0.5–1	1	0.5–1

Hospitals represented in the survey: Erasmus MC-Sophia, Rotterdam; LUMC, Leiden; UMC Utrecht; UMC Groningen; Our Lady's Children's Hospital, Crumlin; Children's Hospital Bambino Gesù, Rome; Royal Brompton Hospital, London; Royal Children's Hospital, Melbourne; University Hospital, Leuven; University Hospital La Paz, Madrid; Starship Children's Hospital, Auckland; Hospital for Sick Children, Toronto; German Heart Centre, Munich; and Queen Silvia Hospital Gothenburg, Memorial Hospital – Child Health Centre, Warsaw. PO, per oral; PR, per rectal.

Table 2 Results of the international survey for type and dose of sedatives in children after cardiac surgery

	Neonates 0–28 days		Infants 29 days–2 years	
Medication	**Use in hospitals (n)**	**doses**	**Use in hospitals (n)**	**doses**
Midazolam IV bolus mg/kg	12	0.05–1.5	12	0.05–1.5
Midazolam IV mg/kg/h	15	0.06–4	15	0.06–0.5
Clonidine IV bolus mcg/kg	3	0.5–2	3	0.5–2
Clonidine IV mcg/kg/h	7	0.5–2	7	0.5–2
Lorazepam PO mg/kg	3	0.05	3	0.05
Propofol IV bolus mg/kg	3	1	3	1
Propofol IV mg/kg/h	3	1–6	3	1–6
Esketamine IV bolus mg/kg	1	0.5–1	1	0.5–1
Esketamine IV mg/kg/h	1	0.5–1.5	1	0.5–1.5
Chloral hydrate IV mg/kg	3	10–50	3	10–50
Chloral hydrate NG mg/kg	1	12.5–25	1	12.5–25
Promethazine mg/kg	1	0.5–1.5	1	0.5–1.5
Chlorpromazine mg/kg	2	0.5–1.5	2	0.5–1.5

Hospitals represented in the survey: see table 1.
NG, nasogastric; PO, per oral.

therapy in patients returning from the operating room with an open sternum.

Analgesics

Opioids were the preferred analgesic; morphine was the opioid of choice in 13 (87%) of the hospitals. Dosing ranged from 10 to 60 mcg/kg/h for a continuous infusion and from 50 to 500 mcg/kg for a bolus dose. Morphine was supplemented with a second analgesic in 73% of hospitals, either as standard practice or rescue therapy. The primary choice of analgesics varied between hospitals but did not differ between age groups within hospitals. Most drugs were dosed according to weight. However, overall dosing ranges in neonates tended to be lower compared with infants and children. Furthermore in children over 2 years of age more alternative analgesic drugs were reported as used per protocol in some hospitals, namely oxycodone, nalbuphine and diclofenac.

Dexmedetomidine could be considered a sedative but was reported as an analgesic in the survey and therefore reported as such.

Sedatives

Midazolam was the primary sedative in 100% of hospitals, either as a bolus or a continuous infusion. Eight hospitals (53%) reported routine use of sedatives with pain treatment. The other hospitals only started sedatives in response to discomfort. Of eight hospitals who routinely use sedatives with pain treatment, six used morphine as primary analgesic in an average dose of 10–30 mcg/kg/h with one outlier using morphine from 30 to 60 mcg/kg/h, in neonates and infants, respectively. Two other hospitals who routinely use sedatives with pain treatment used piritramide (dose 1.2 mg/kg/day) and fentanyl (dose 5 mcg/kg/h) as primary analgesics. Average dosing of morphine in hospitals without routine sedation was 5–40 mcg/kg/h. Overall morphine dosing in hospitals that use standard sedatives are comparable or lower than hospitals that do not use standard sedatives.

Sedatives were used as per protocol or at the attending physician's discretion. Treatment strategies between neonates and infants varied less for sedatives than for analgesics. There were no reported differences in choice of drugs and dosing between infants 29 days–2 years and children older than 2 years.

Sedation scores

All hospitals used a validated pain and sedation score. Table 3 shows the different scores used. Pain and sedation was assessed using a total of six different paediatric pain and four different sedation scores. Eleven (73%) of the 15 hospitals used the COMFORT-Behavioural scale and Numeric Rating Scale (NRS) for pain and sedation. Frequency of pain and sedation assessment varies between hospitals. Reassessment after an intervention, either medical or non-medical, was reported by two respondents.

Each centre reported the use of a local protocol to guide analgosedation after cardiac surgery.

DISCUSSION

The choice and dosing regimens of analgesics and sedatives after cardiac surgery in children varied extensively

Table 3 PD tools reported in the survey

Scale	Validated age range	Number of centres	How often assessed first 72 hours after surgery? Minimal and maximal
Pain assessment			
FLACC (33)	2 months–7 years	2	n.s.
CRIES (34)	0–28 days	1	n.s.
COMFORT-B scale (35-37)	0–3 years	1	n.s.
VAS pain obs	0–3 years	7	8 hourly, after bolus
NRS pain obs	0–3 years	4	2–4 hourly, after bolus
LLanto scale		1	n.s.
Sedation assessment			
NISS (38)	0–18 years	2	8 hourly, after bolus
COMFORT-B scale (38)	0–18 years	11	4–8 hourly, after bolus
Brussels Sedation Scale (39)	Adults	1	n.s.
Ashworth scale (40)		1	n.s.

COMFORT-B, COMFORT-behavioural scale; CRIES, Crying, Requires O2 for SaO2 <95%, Increased vital signs (blood pressure and heart rate), Expression, Sleepless; FLACC, Face, Legs, Activity, Cry, Consolability; LLANTO SCALE, llanto, actitud, normorrespiración, tono postural y observación (crying, attitude, respiratory pattern, muscle tone and facial); NISS, Nurses' Interpretation of Sedation Score; NRS, Numeric Rating Scale pain observation; n.s., not specified; VASobs, Visual Analogue Scale observation.

across the globe. Opioids were the analgesics of choice. Morphine was the preferred analgesic drug, with a wide range of doses, both for continuous infusion and bolus administration in both the neonatal age group and in older infants and children. Morphine was supplemented by a second analgesic drug in 73% of the surveyed hospitals. Differences between local protocols were evident in all age groups; however, more variation in analgesics and sedatives was found in infants and children as compared with neonates. The underlying cardiac diagnosis, severity score or type of surgery did not result in different treatment algorithms or dosing regimens. Eight hospitals routinely used a sedative in combination with pain treatment, all other hospitals started sedatives only in response to a clinical need for sedation.

The reported use of drugs are comparable with those described by Wolf in 2011 and reflect in part the guidelines from the Royal College of Paediatrics and Child Health (UK) as well as the guidelines from the Association of Paediatric Anaesthetists of Great Britain and Ireland.[7 8] The recent consensus statement by Lucas *et al* describes the pharmacotherapies currently available to manage pain and sedation in paediatric cardiac critical care patients and summarises dosing recommendations from available literature.[13] Lucas and colleagues conclude that a more individualised analgesic and sedative treatment strategy is necessary to provide optimal care without adverse effects resulting from pharmacotherapy.

This need for individualised dosing is possibly reflected in the reported wide range of dosing for morphine with the highest morphine infusion rate of 60 mcg/kg/h and largest bolus of 500 mcg/kg in the participating centres as well as the use of adjuvant analgesics and sedatives. However, doses mainly differed between hospitals, not within hospitals. Differences in morphine dosing could also reflect differences in local practices and preferences between hospitals rather than individualised dosing regimens based on clear PD endpoints.

Ideally we would like to predict individual morphine requirement beforehand and better categorise the efficacy of adjuvant or alternative analgesics to minimise adverse effects. Advances towards precision medicine have been made for morphine in non-cardiac surgery patients mainly focusing on the patients' size, maturation and organ function.[6 15 16] By using information from PK/PD studies on morphine consumption after cardiac surgery, we aim to individualise and assess treatment effect by regular pain and sedation assessment and tracking of adverse drug reactions. However, PK parameters of analgesics and sedatives, or potential PK alterations in children after cardiac surgery are currently incomplete. Changes of clearance and volume of distribution would be expected in this cohort, dependent on the use of the CPB, age and underlying pathology. For remifentanil,[17 18] dexmedetomidine,[19 20] clonidine[21] and ketamine,[22] studies have been published within the last 10 years with PK parameters in neonates and children after cardiac surgery. However, these studies show conflicting results on PK alterations and most lack PD endpoints to assess efficacy, making it difficult to implement dose recommendations in clinical practice.

Due to polypharmacy, it is difficult to assess the efficacy and safety of individual drugs. Our survey showed that a multimodal drug approach is often used for analgesics and sedatives. The challenge is to determine how these drugs interact.[23 24] The combination of sedatives and opioids may contribute to oversedation, which is highly undesirable and could lead to longer PICU stay, longer ventilation times, drug tolerance and dependence.[25]

PD aspects after cardiac surgery are rarely described in literature, making interpretation of PK knowledge clinically limited. Validated PD scoring tools were used in our survey hospitals, mainly the COMFORT-B scale (73%), VAS (47%) and the NRS (26%). Interpretation of some scores can be problematic, because of poor validation in neonates and infants after cardiac surgery. Moreover, items for rises in blood pressure and heart rate are less useful in children after cardiac surgery because of the use of inotropic agents.

This study has several limitations. Clinical practice may deviate from protocol that might not be reflected in the survey. Also, the participating hospitals are all based in developed countries, mostly in Europe. Although the data from our study seem to reflect the day-to-day practice of analgosedation after cardiac surgery in children, we cannot rule out that some selection of the hospitals that were approached and that responded may have an effect on the diversity of the findings. A larger survey might increase the amount of variability or show more consensus within countries.

CONCLUSION

This survey shows that there is large variability in both dosing and choice of analgosedative drugs used in paediatric postcardiothoracic surgery patients especially between hospitals. This large variability reflects the complexity of analgosedation in these vulnerable patients and highlights the need for clinical studies combining PK with validated PD outcomes. Such studies are necessary to understand specific changes in this population and permit evidence-based and personalised treatment protocols.

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